REMARKS

Claims 1, 2, 3 and 5 have been amended to clarify by replacing the phrase "containing substances" with the term "compounds". The symbol ">" in the definition of R^2 in claim 16 means a -CO- bridge. In the interest of furthering prosecution the ">" symbol has been replaced with -CO-. Claim 16 formula XI has been amended to correct the formula by adding the placement of the substituent R^2 . Support for this can be found for example at page four, lines 18-23 of the specification which points out that the paramagnetic perfluoroalkyl-containing compounds of the invention are described in DE 19603033 and WO 97/26017. Formula XI on page 141 of the WO 97/26017 publication and on page 167 of the English translation depicts the correct formula for XI showing the placement of the R^2 group. Originally presented claim 16 recites that R^2 has the meaning of R^1 in claim 6. Claim 16 presented in the preliminary amendment of 6 September 2001 defined the R^2 groups but further included definitions of R^2 which included (in error) portions of the linker element. The erroneous portion of the R^2definition from claim 16 has been deleted.
Support for new claim 39 can be found for example at page 27, line 4. Support for new claim 40 can be found for example at page, 27 and in the examples.

Rejections under 35 USC §112, second paragraph

Applicants submit the rejection of claims 1-3, 5 under 35 USC 112, second paragraph, is moot in view of the amendments above. The rejection of claim 16 is respectfully traversed.
The term "optional" in claim 16 is fully conventional alternative claim language (See Ex parte Cordova, 10 USPQ2d 1949 (Bd. Pat. App. & Inter. 1989) and Ex parte Wu, 10 USPQ2d 2031 (Bd. Pat. App. & Inter. 1989). Moreover, the term is clear from the context of the paragraph and it is submitted that the term is thus definite on its face.

The claims satisfy the requirements of the second paragraph of the statute, and withdrawal of this rejection is respectfully requested.

Rejections under 35 USC §103, second paragraph

Claims 1-5, 16 and 23-25 have been rejected under 35 USC 103 as being unpatentable over

Platzek et al. (WO 97/26017) in veiw of Millius et al.(New Journal of Chemistry 1992). This rejection is respectfully traversed.

In the Office Action , the Examiner has pointed out that each of the two individual (perfluoroalkyl-containing) components that form the galenical formulation of the present invention are known in the prior art and that each are known to be used for MR imaging. It is alleged that the resulting combination is also suitable as an MRI contrast media and that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose.

However, it would not be obvious to combine the two types of perfluoroalkyl compounds, one being paramagnetic and the other diamagnetic. The former type of compound acts as a contrast agent because its paramagnetism has an effect on, e.g., in the typical MRI procedure, the hydrogen atoms in water. In such images, it is not the paramagnetic agent which is seen; rather, it is the hydrogen atoms in water and tissue which are depicted. The paramagnetic agent merely influences the nature of the image which can be seen for such hydrogen atoms. On the other hand, with a diamagnetic compound, there is no similar effect. Rather, the diamagnetic compound itself is imaged in a negative way, i.e., one observes a void on an image due to the presence of the diamagnetic compound. (These concepts will be slightly different for both types of compounds when H-atoms are contained. With respect to F-based imaging, there is no motivation at all of record to combine the claimed agents.) With respect to the diamagnetic agents, see pages 249-250 of Mattrey, a copy of which is attached.

Thus, the Kerkoven case is not relevant. Compounds having such different functions are not obvious to use in combination. As a result, there is no obviousness of the claimed combination.

Merely, as a supplement, applicants are providing a summary of certain experiments which have been conducted. These show that the combination of the invention produces results which are unexpected in comparison to a paramagnetic compound alone. Since this showng is not necessary to patentability, applicants are not submitting it in the form a declaration. However, if the examiner wishes such a declaration, the undersigned will be happy to comply.

For all of the above reasons, it is respectfully submitted that the prior art, considered as a whole, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. '103 should be withdrawn.

Based on the above remarks, Applicants submit that the claims are in a form suitable for allowance and patentable over the cited references. Therefore, withdrawal of the rejections and allowance of these claims are earnestly submitted.

Respectfully submitted,

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Date: 26 February 2003
jjb:

MARKED UP VERSION SHOWING CHANGES MADE

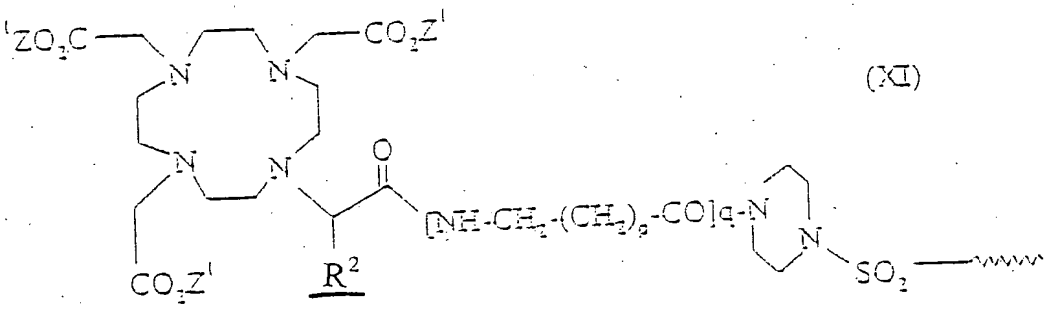
1. **(Amended)** A galenical formulation comprising paramagnetic perfluoroalkyl and diamagnetic perfluoroalkyl-~~containing substances~~ compounds.

2. **(Amended)** A formulation according to claim 1, wherein the ratio of the paramagnetic perfluoroalkyl compound to the diamagnetic perfluoroalkyl-~~containing substances~~ compound ~~lies between~~ is 5:95 and 95:5.

3. **(Amended)** A formulation according to claim 1, wherein the paramagnetic perfluoroalkyl and diamagnetic perfluoroalkyl-~~containing~~ compounds are present dissolved in an aqueous solvent.

5. **(Amended)** A formulation according to claim 4, wherein molecule portion A stands for a group L-M, ~~whereby~~ wherein L stands for a linker and M stands for a metal complex that ~~consists~~ comprises ~~of~~ an open-chain or cyclic chelating agent~~,~~ ~~which as~~ having a central atom ~~contains an atom~~ of atomic ~~numbers~~ number 21-29, 39, 42, 44 or 57-83.

16. **(Amended)** A formulation according to claim 5, wherein metal complex M is a complex of general formula XI



(XI)

in which

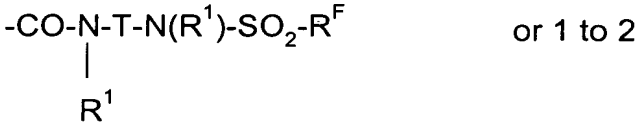
Z^1, independently of one another, mean a hydrogen atom or a metal ion equivalent of atomic numbers 21-29, 39, 42, 44 or 57-83,

and whereby p means the numbers 0 to 10, q and u,

independently of one another, mean the numbers 0 or 1, and

R^2 means a hydrogen atom, a methyl group, a $-CH_2-OH$ group, a $-CH_2-CO_2H$ group

or a C_2-C_{15} chain, which optionally is interrupted by 1 to 3 oxygen atoms, 1 to 2 ~~>CO~~ -CO- groups or an optionally substituted aryl group and/or is substituted with 1 to 4 hydroxyl groups, 1 to 2 C_1-C_4 alkoxy groups, 1 to 2 carboxy groups. ~~, or a straight chain, branched, saturated or unsaturated C_2-C_{30} carbon chain, which optionally contains 1 to 10 oxygen atoms, 1 to 3 NR^+ groups, 1 to 2 sulfur atoms, a piperazine, a $CONR^+$ group, an NR^+CO group, an SO_2 group, an NR^+CO_2 group, 1 to 2 CO groups, a group~~



~~optionally substituted aryls and/or is interrupted by these groups and/or is optionally substituted with 1 to 3 OR^+ groups, 1 to 2 oxo groups, 1 to 2 $NHCOR^+$ groups, 1 to 2 $CONHR^+$ groups, 1 to 2 $(CH_2)_p$-CO_2H groups, 1 to 2 groups $(CH_2)_p$-$(O)_q$-CH_2CH_2-R^F.~~

Example 1: Relaxivity

The T1 and T2 relaxation times of plasma with increasing concentrations of MRT contrast media (0.05 to 0.25 mmol of Gd/I) were measured at 0.47 T and at a temperature of 40°C with use of an NMR pulse spectrometer (Minispec PC 20; Bruker, Rheinstetten, Germany).

The T1 and T2 relaxation times of a galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and **3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid** (proportion of 20 mol%) were considerably higher compared to pure **complex I**.

Substance	Medium	Relaxivity [l/(mmol*s)]	
		R1	R2
Galenical formulation that consists of complex I and 3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid	Plasma	32.7	42.4
Complex I	Plasma	28.2	33.0

Example 2: Organ Distribution After Intravenous Administration of the Contrast Medium in Prostate-Cancer-Bearing Rats

After intravenous administration of 200 μmol of total gadolinium/kg of body weight of a galenical formulation that consists of **complex III** (Gd-GlyMe-DOTA-trimer-perfluorooctyl-oxadecylamide) and the **compound of Example 11a** (mannose-perfluorooctylsulfonamide; proportion 40 mol %) in rats (Cop-inbreeding Dunning R3327 MAT-Lu prostate cancer i.m.-implanted 12 days earlier), the metal content in the entire organism was determined 24 hours after administration (MW ± SD, n = 3). The galenical formulation in this case has a smaller Gd content (8.3% of the administered dose) compared to the pure **complex III** (9.2% of the administered dose), i.e., the galenical formulation is better eliminated from the body.

Example 3: Signal Increase (Enhancement) in Healthy Lymph Node Tissue by Means of MRT After Intravenous Administration of the Contrast Medium in Guinea Pigs

The table shows the enhancement (percentage of signal increase in comparison to the precontrast value) that was achieved by means of MRT in popliteal, inguinal and iliac lymph nodes at the time of 60 minutes after intravenous administration of 100 μmol of Gd/kg of body weight of a galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and the **compound of Example 11a** (mannose-perfluorooctylsulfonamide; proportion of 40 mol %), as well as a galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and **3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid** (proportion of 40 mol %), in comparison to the pure **complex I** in guinea pigs with stimulated lymph nodes (complete Freund adjuvant; in each case 0.1 ml i.m. in the right and left upper and lower legs; 2 weeks before the administration of test substance) (MW ± SD, n = 3). In this experiment, a clear advantage of the galenical formulations in comparison to the pure complex was also shown.

Substance	Enhancement [%] in Lymph Nodes 60 minutes p.i.		
	Popliteal	Inguinal	Iliac
Complex I	107 ± 14	117 ± 36	88 ± 9
Galenical formulation that consists of complex I and a compound of Example 11a	170 ± 38	123 ± 20	122 ± 13
Galenical formulation of complex I and 3-oxa-2H2H4H4H5H5H-perfluorotridecanoic acid	195 ± 26	141 ± 14	148 ± 25

Example 4: Lymph Node Concentration in Guinea Pigs After Interstitial Administration

A galenical formulation that consists of **complex I** (Gd-GlyMe-DOTA-perfluorooctyl-sulfonamide) and the **compound of Example 11** (mannose-perfluorooctylsulfonamide; proportion of 40 mol %) as well as the pure **complex I** were

studied 30 minutes after subcutaneous administration (10 μmol of total gadolinium/kg of body weight, hind paw s.c.) in guinea pigs with stimulated lymph nodes (complete Freund adjuvant; in each case 0.1 ml i.m. in the right and left upper and lower legs; 2 weeks before administration of the test substance) with respect to their lymph node concentration in three successive lymph node stations (popliteal, inguinal, iliac). In this connection, the results listed below (determination of the gadolinium concentration by means of ICP-AES, MW ± SD, n =3) were obtained:

Progress in Radiology

Perfluorooctylbromide: A New Contrast Agent for CT, Sonography, and MR Imaging

Robert F. Mattrey[1]

Perfluorochemicals are a class of compounds composed entirely of carbon and fluorine atoms. They were made famous when Clark and Gollan [1] demonstrated their oxygen-carrying potential by submerging normal mice in the liquid for an extended period of time. These mice suffered no ill effects while they were submerged or afterward [1]. Perfluorochemicals, like oil, are immiscible with water and cannot be given intravenously unless emulsified [2]. Fluosol-DA (Alpha Therapeutics Corp., Los Angeles, CA) and PFOB-100% (Fluoromed Pharm, La Mesa, CA) are two emulsions that have been given intravenously to human subjects [3, 4].

Perfluorooctylbromide (PFOB), a fluorochemical in which one bromine atom is substituted for fluorine, is radiopaque on radiography and CT [5–10]. PFOB has been used in human subjects in its neat form (pure unemulsified liquid) for radiography of the gastrointestinal tract and for bronchography (Long DM, unpublished data). IV perfluorochemical emulsions given to animals [11–13] and humans [14] are effective sonographic contrast agents. Because these compounds, in the neat form, have no hydrogen atoms, they are effective negative oral contrast agents for MR imaging [15, 16]. These agents can also be imaged with MR when coils are tuned to the Larmor frequency of the ^{19}F nucleus [17]. Clinical trials with IV PFOB as a CT and a sonographic contrast agent have begun in Europe. Preliminary reports are extremely encouraging [4].

Physical Properties, Pharmacokinetics, and Toxicity of PFOB

Perfluorochemicals, including PFOB, are inert and have high gas solubility, low surface tension, and very low toxicity when ingested or inhaled [18, 19]. Because of these unique properties they are used extensively in industry as cleansers, lubricants, and propellants [18]. These compounds actually behave like a liquefied gas. Some are extremely volatile, like freon, whereas others are extremely stable. They accumulate in human tissues when inhaled, ingested, or given intravenously. The length of time they remain in the body is related to their molecular weight and vapor pressure (volatility); the more volatile they are the shorter their half-life, which can range from minutes to years [20, 21]. Those with very short half-lives (hours) cannot be used intravenously because they produce pulmonary emphysema as they evaporate out of the pulmonary capillaries into the interstitium [21]. IV PFOB-100%, given to rats at a dose of 1.5 g/kg, has a half-life of 3 days, which is long enough to be safe and short enough to be practical [22]. Fluosol-DA 20%, the first perfluorochemical used in humans intravenously, consists of two perfluorochemicals, perfluorodecalin and perfluorotripropylamine (their half-lives are 6 and 63 days, respectively) [21].

PFOB, which is twice as dense as water, is emulsified in pure lecithin to produce 100% weight per volume emulsion

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AJR 152:247–252, February 1989 0361–803X/89/1522–0247

(1 g PFOB in 1 ml emulsion) with particle sizes 0.1- to 0.2-μm in diameter [23]. These particles, unable to leak out of normal capillaries, are limited to the intravascular space. PFOB is removed from blood by two competitive mechanisms, phagocytosis by the reticuloendothelial system and evaporation through the lung. In rats, the PFOB half-life in blood was approximately 6 hr after the infusion of 2.5 g/kg [22]. In rats, 99.8% of the IV PFOB dose is eliminated in the expired air. The remainder is eliminated in feces during the first few days, probably from bile excretion, and none is eliminated in urine [22]. Early clinical data from the European trials suggest a shorter blood half-life in man.

IV PFOB is eliminated without breakdown of its chemical structure. No acute hemodynamic effects of the lecithin-based 100% PFOB emulsion occurred when 1 g (1 ml)/kg was given as an IV bolus to dogs (Mattrey RF, unpublished data). The 7-day LD_{50} of PFOB in rats is 45 g/kg with an LD_{50} to diagnostic dose ratio of 22:1 [22]. No subacute or chronic toxicity of PFOB is expected.

More than 95% of the oral PFOB dose is excreted by the gastrointestinal tract within 24 hr [5]. No LD_{50} could be measured in rats when dosages in excess of 64 ml/kg were ingested [5, 24]. PFOB has been taken orally by approximately 60 human subjects at dosages of 2–12 ml/kg. Extensive laboratory studies before and at various time intervals up to 3 days after PFOB ingestion showed no effect [15, 16]. Although some absorption occurs after ingestion, minuscule levels are detectable in tissues that are five orders of magnitude smaller than would be found if 1 g/kg were given intravenously. An IV dose of 1 g/kg has no detectable toxic effect [22].

Computed Tomography

Although urographic contrast agents are ideal for renal CT scanning, they are suboptimal for imaging the blood pool and various organs on CT. These agents are lost to the extravascular space because they quickly diffuse into and equilibrate with the interstitial fluid. Because PFOB remains intravascular, the dose can be titrated to provide the blood enhancement desired on CT, and the degree of enhancement will be the same throughout the arteries, veins, and cardiac chambers (Fig. 1) [9]. With the 6-hr blood half-life of PFOB, this enhancement persists long enough to allow ample time for CT imaging. Tissues enhance to a degree commensurate with their blood volume [25]. Blood-pool enhancement of tissues with PFOB on CT is comparable to labeled RBC blood-pool scanning in nuclear medicine. PFOB on CT should allow the differentiation of intrahepatic tumors from hemangiomas, because intrahepatic tumors have less blood than liver does and hemangiomas are essentially a blood pool. This hypothesis would of course require testing in the clinical setting.

EOE-13 (ethiodized oil emulsion), like PFOB, is taken up by the reticuloendothelial system of the liver and spleen [8, 26]. EOE-13 does not enhance blood vessels. It has a sensitivity of 90% for the detection of liver tumors, which is considered to be the best of all CT techniques [27]. The reason for the less than perfect sensitivity is because small lesions are confused with comparable-sized intrahepatic vessels and vice versa [28]. However, unlike EOE-13 enhancement, the simultaneous enhancement of the vascular space with PFOB renders lesions the only unopacified structures within the liver (Fig. 2), potentially providing greater than the 90% sensitivity in the detection of liver lesions achieved with EOE-13.

Within minutes to hours after PFOB is given, enhancement of abscess wall and tumors begins; enhancement peaks at 1–4 days. Accumulation of PFOB in these sites is thought to occur by either transcapillary leak through abnormal neoplastic or inflammatory vascular beds, accumulation of PFOB-filled macrophages, or both. That transcapillary leakage occurs is evidenced by tumor rim enhancement minutes after infusion [29] and the presence of PFOB particles in the perivascular space when lecithin is stained with a fat stain [17]. By 48 hr, all of PFOB in these sites is within macrophages that are then present in large numbers when compared with controls [8, 10]. It is not clear how these PFOB-filled macrophages accumulate in lesions. They may have taken up PFOB elsewhere, become activated as has been suggested [30], and accumulated in immunologically active sites; or they may have been residents of these sites or recruited to these sites to phagocytose the PFOB particles present in the interstitium.

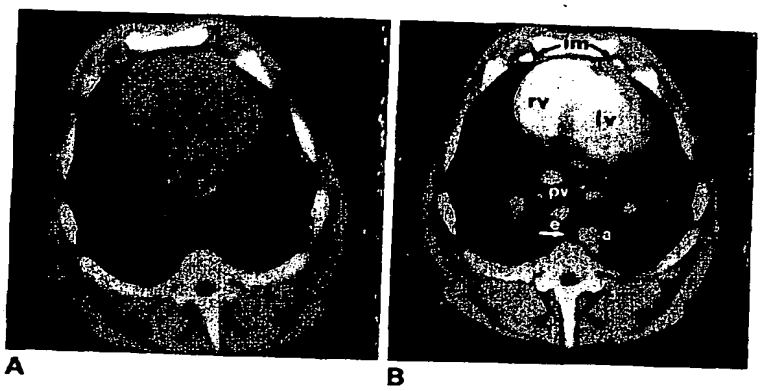

Fig. 1.—Transverse CT scans at level of heart in pig before and after IV administration of 5 g/kg perfluorooctylbromide (PFOB).

A, Before PFOB. All vascular and nonvascular structures are isodense.

B, 50 min after PFOB. All vascular structures are markedly enhanced to same degree, including intrapulmonary vessels (pv). There is marked enhancement of internal mammary vessels (im). Enhanced descending aorta (a) is recognized from esophagus (e). rv = right ventricle; lv = left ventricle.

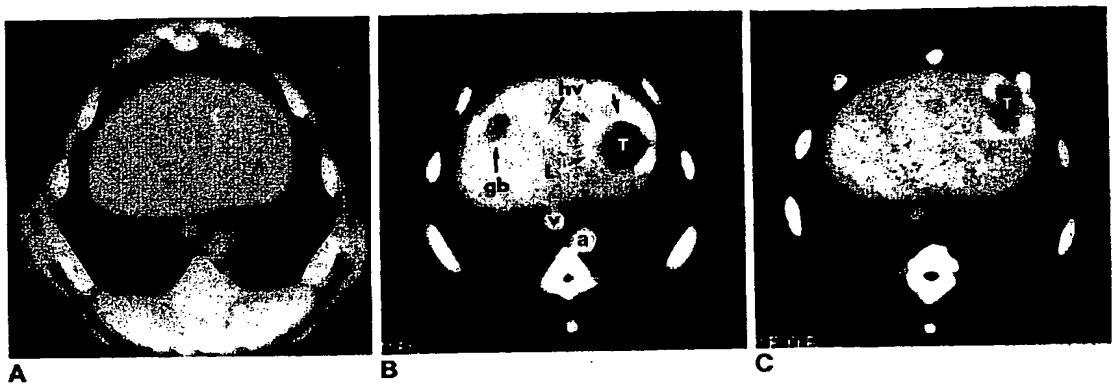

Fig. 2.—Transverse CT scans of rabbit at level of V×2 tumor implanted in liver.
A, Before perfluorooctylbromide (PFOB). Tumor (T) is isodense relative to liver and paraspinal muscles.
B, 6 min after 5 g/kg PFOB. Liver (L) and blood vessels, including intrahepatic veins (hv), enhance significantly relative to tumor and paraspinal muscles. There is a faint hypervascular tumor rim (*small arrows*).
C, 48 hr later. Tumor rim has become hyperintense relative to liver (*arrows*).
a = aorta; v = vena cava; gb = gallbladder.

Lesion enhancement has been documented by both CT and sonography after the administration of PFOB [8, 10–13, 29]. In fact, it appears that PFOB accumulates in any region where macrophages are found, including tumors [8, 11, 12, 14, 29], abscesses [10, 31], and injured [32] or infarcted [13] tissues. This leads to enhancement of the area on CT in proportion to the degree of inflammation [32]. An application of great clinical potential may be the use of PFOB as a CT contrast agent to improve the detection of abscesses. In rabbits in which hepatic and peritoneal abscesses were induced, PFOB produced dense enhancement of abscess wall on CT 2 days after infusion of the compound [10]. Although liquefied centers of hepatic abscesses could be seen without PFOB, PFOB made it possible to determine the extent of the inflammation (Fig. 3). Although the peritoneal abscesses were not visible on CT without PFOB, they were all identified after PFOB administration [10].

Sonography

Perfluorochemicals are effective contrast agents for sonography [11, 12]. The echogenicity of perfluorocarbons is due to their high density (1.9 g/ml) and low acoustic velocity (600 m/sec), imparting an acoustic impedance difference of 30% with tissues. Because impedance difference determines the brightness of the echo, and because the impedance of tissues (except for fat) differ by 1–5%, perfluorochemicals are highly reflective. Thus, the presence of PFOB particles in tissues increases the number and brightness of interfaces and therefore echogenicity.

PFOB enhances tissues during its vascular phase immediately after infusion [29]. The degree of enhancement is commensurate with the degree of perfusion. Hypovascular renal tumors that have the same or greater echogenicity than the kidney become less echogenic immediately after PFOB infusion [29]. This is also true of liver tumors (Fig. 4). Increased echogenicity in proportion to the degree of vascularity may allow sonography to be used to estimate the degree of tissue perfusion, visualize areas of infarction, and tumors.

Doppler signals and their color rendition enhance significantly as a result of PFOB [33], which lasts for hours because of the long blood half-life of PFOB. Doppler signals, including color, become detectable from submillimeter vessels as well as vessels not seen on the gray-scale image [33]. This capability should have a significant impact on deep Doppler applications, where small or deep vessels reflect weak signals.

Perfluorochemicals also enhance the liver and spleen because of their uptake by the reticuloendothelial cells for at least 2 days after their administration [11–14]. In humans, Fluosol-DA 20% produced significant liver and spleen enhancement 24 hr after a dose of 2.4 g/kg, allowing the visualization of unenhanced tumors [14].

As with CT, macrophages that accumulate in lesions become visible sonographically. In patients, the IV administration of Fluosol caused significant rim or diffuse echogenic enhancement of colonic, pancreatic, and gastric liver metastases at dosages of 1.6 and 2.4 g/kg, allowing the visualization of previously missed lesions [14].

MR Imaging

PFOB as an Oral MR Contrast Agent

Neat perfluorocarbons have potential as MR oral contrast agents because (1) lacking hydrogen, they cause no MR signal, and therefore, like air, they darken bowel lumen on both T1- and T2-weighted images; (2) being immiscible with water, they produce a signal void that is independent of bowel content; (3) they have a more rapid transit through bowel than

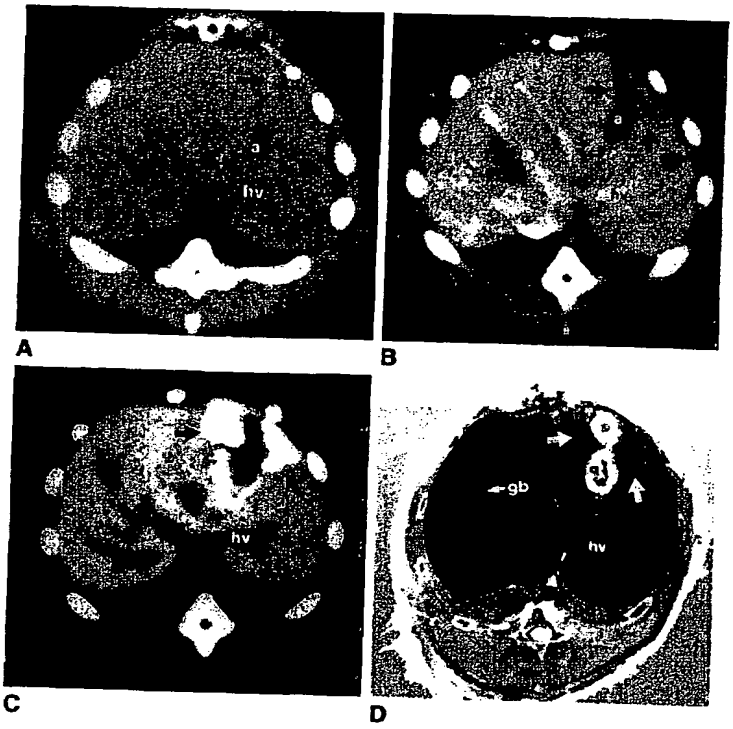

Fig. 3.—Transverse CT scans of rabbit at level of abscess in liver.

A, Before perfluorooctylbromide (PFOB). Faint calcification is seen at abscess (a) margin (*arrow*).

B, 5 min after 5 g/kg PFOB. Liver and blood vessels, including intrahepatic veins (*hv*), enhance significantly relative to abscess, phlegmon about abscess (*arrows*), and paraspinal muscles. Phlegmon does not enhance significantly.

C, 48 *hr* later. Dense enhancement of phlegmon (*arrows*) extends beyond abscess wall. Intrahepatic vessels are less dense than liver.

D, Anatomic section at approximate level of C shows phlegmon (*arrows*) extending beyond confines of abscess.

gb = gallbladder.

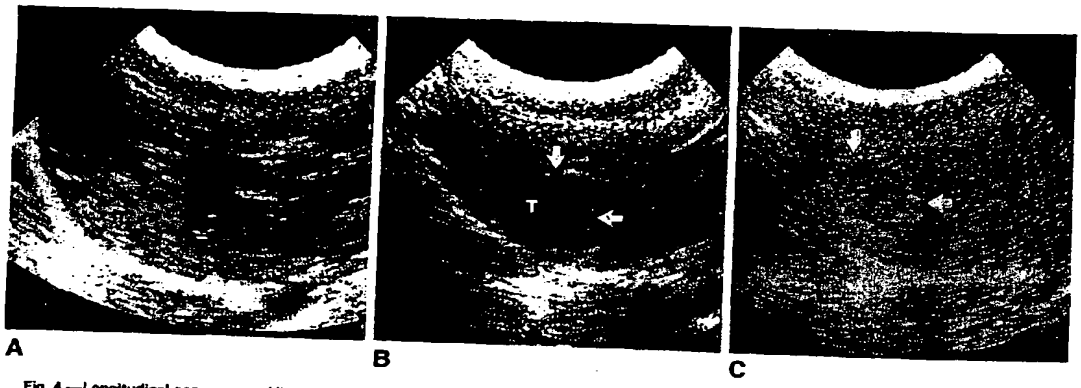

Fig. 4.—Longitudinal sonograms of liver at level of V×2 tumor of rabbit in Fig. 2.

A, Before perfluorooctylbromide (PFOB). Tumor (T) is hyperechoic relative to surrounding liver.

B, 30 min after 5 g/kg PFOB. Tumor is hypoechoic relative to liver. There is faint rim enhancement (*arrows*).

C, 48 *hr* later. Tumor rim is echogenic (*arrows*).

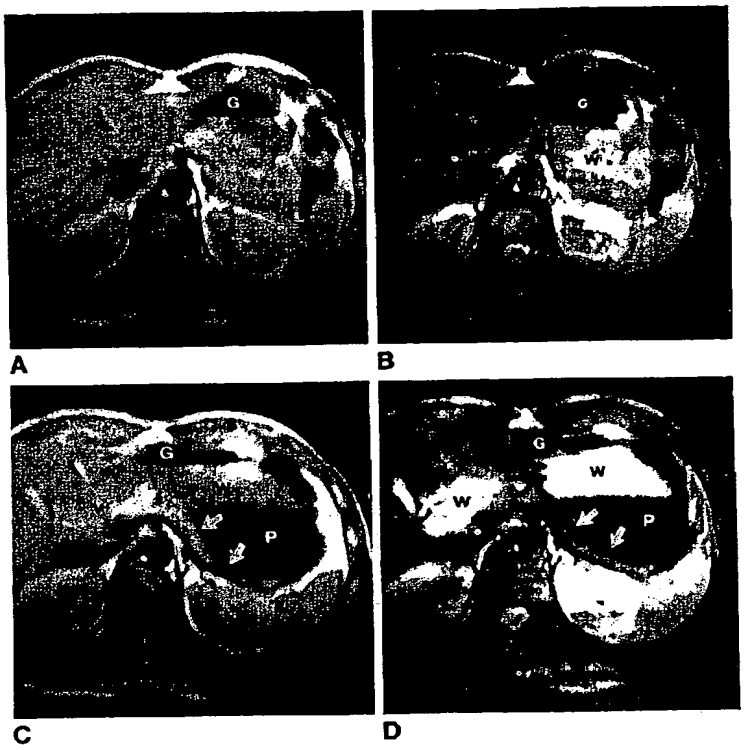

Fig. 5.—Transverse MR images at level of pancreas of volunteer before and after ingestion of 500 ml neat perfluorooctylbromide (PFOB).

A and *B*, Hydrogen-density (2000/20) (*A*) and T2-weighted (2000/70) (*B*) images before PFOB ingestion. Pancreas is not visible because of water (W) in gastric fundus.

C and *D*, Hydrogen-density (*C*) and T2-weighted (*D*) images obtained with same technique 5 min after PFOB ingestion. Clear visualization of pancreas (*arrows*) contrasts with PFOB-filled gastric fundus. Air-fluid-fluid level with water (W) floating between gas (G) and PFOB (P).

barium or Hypaque because of their low surface tension [5]; and (4) they are tasteless, odorless, and have no side effects [5, 24]. The use of PFOB was shown to be feasible in rats and humans [15]. PFOB significantly darkened bowel lumen on T1-weighted, hydrogen-density, and T2-weighted images (Fig. 5) [16].

MR Imaging of the ^{19}F Nucleus

Fluorine is the next best nucleus for MR applications after hydrogen, because it has 100% natural isotopic abundance and has an 83% sensitivity relative to hydrogen. ^{19}F in PFOB can be imaged to show the vascular pool, liver, spleen, and macrophage collections [17, 34].

^{19}F MR imaging or spectroscopy can be used to estimate tissue oxygen tension percutaneously. Neat PFOB can carry more than twice as much oxygen as whole blood can [2]. Dissolved molecular oxygen is paramagnetic, affecting T1 shortening of ^{19}F [35]. Tissue oxygen tension can be estimated by appropriate MR techniques, because oxygen in perfluorocarbons is carried passively and is in equilibrium with tissue oxygen tension [2], and the ^{19}F relaxation rate is linearly related to oxygen tension dissolved in the perfluorocarbon [35]. Fishman et al. [36] showed signal-intensity changes in various tissues in rats when respired oxygen tension was changed from 20% to 100%. Therefore, these agents can be used to detect ischemic tissues and to monitor the efficacy of therapy. Although this technique is feasible and of great interest, its accuracy and potential utility in vivo have not yet been documented.

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